Enhanced myogenic tone in cerebral arteries from a rabbit model of subarachnoid hemorrhage

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Ishiguro, Masanori, Corey B. Puryear, Erica Bisson, Christine M. Saundry, David J. Nathan, Sheila R. Russell, Bruce I. Tranmer, and George C. Wellman. Enhanced myogenic tone in cerebral arteries from a rabbit model of subarachnoid hemorrhage. Am J Physiol Heart Circ Physiol 283: H2217–H2225, 2002; 10.1152/ajpheart.00629.2002.—Cerebral artery vasospasm is a major cause of death and disability in patients experiencing subarachnoid hemorrhage (SAH). Currently, little is known regarding the fate of cerebral arteries from SAH animals. Cerebral arteries from SAH animals constricted more (two-fold) to pressure within the physiological range of 60–100 mmHg compared with control or sham-operated animals. Pressure-induced constriction (myogenic tone) was also enhanced in arteries from control animals organ cultured in the presence of oxyhemoglobin, an effect independent of the vascular endothelium or nitric oxide synthesis. Finally, arteries from both control and SAH animals dilated as intravascular pressure was elevated above 140 mmHg. This study provides evidence for a role of oxyhemoglobin in impaired autoregulation (i.e., enhanced myogenic tone) in small diameter cerebral arteries during SAH. Furthermore, therapeutic strategies that improve clinical outcome in SAH patients (e.g., supraphysiological intravascular pressure) are effective in dilating small diameter cerebral arteries isolated from SAH animals.

vascular smooth muscle; vasospasm; intravascular pressure; oxyhemoglobin; Triple H therapy

SUBARACHNOID HEMORRHAGE (SAH) is frequently associated with a delayed and sustained vasoconstriction (vasospasm) that has been implicated as a major cause of death and disability in patients who survive the initial events associated with cerebral aneurysm rupture (7, 34). Although a number of agents present in blood may contribute to SAH-induced vasospasm (7), a large body of evidence has suggested a role for oxyhemoglobin. For example, the rise in oxyhemoglobin in the cerebrospinal fluid of SAH patients as a result of red blood cell lysis parallels the development of vasospasm (18, 25). In primates, SAH-induced vasospasm can be mimicked by intracisternal injection of purified oxyhemoglobin in a manner comparable to the injection of whole blood (21). Acute exposure of oxyhemoglobin has also been demonstrated to contract cerebral arteries during SAH. Furthermore, therapeutic strategies for the treatment of SAH-induced vasospasm, including free radical generation (29), enhanced synthesis of vasoconstrictor metabolites of arachidonic acid (15), release of ATP (39), inhibition of K+ channels (11, 15, 28), enhanced production of endothelin-1 (40), and activation of a number of kinases (1, 9, 19, 26).

Despite progress in SAH research, current therapeutic strategies employed in the treatment of cerebral vasospasm are less than ideal. The current mainstay in the prevention and treatment of SAH-induced vasospasm is a combination of hypervolemia, hemodilution, and hypertension termed “Triple H or HHH therapy” (2, 33). During Triple H therapy, systemic systolic blood pressure in patients is often increased to 180–220 mmHg. Whereas often effective in alleviating the symptoms of vasospasm, Triple H therapy is associated with significant risks to the patient, including heart failure, cerebral edema, electrolyte imbalances, and additional intracranial bleeding (23, 33).

A major obstacle in the development of therapeutic strategies for the treatment of SAH-induced vasospasm may be that most studies have relied on angiography to assess vasospasm in large diameter cerebral arteries, and thus little is known regarding the fate of small diameter (100–200 μm) arteries during SAH. There is not always a good correlation between angiographic vasospasm and the severity of symptomatic neurological deficits in patients that have suffered cerebral aneurysm rupture (13, 24, 33). One possible
explanation for the discrepancy between angiographic vasospasm and symptomatic vasospasm may relate to the inability of angiography to evaluate arteries <1 mm in diameter. Small diameter arteries play a critical role in the control of cerebral blood flow. Under physiological conditions, small diameter cerebral arteries exist in a partially constricted state that allows various metabolic, humoral, and/or neurogenic factors to increase or decrease arterial diameter to match cerebral blood flow with tissue demand (14). Intravascular pressure appears to be responsible for this basal level of cerebral artery constriction, a phenomenon often referred to as myogenic tone (3, 14).

The objective of the current study was to examine myogenic- or pressure-induced constriction in small diameter cerebral arteries by using an animal model of subarachnoid hemorrhage. This study provides evidence for enhanced myogenic tone in cerebral arteries from SAH animals subjected to a physiological range of intravascular pressures, a phenomenon that can be mimicked by organ culturing cerebral artery segments with oxyhemoglobin. In addition, we observed that as intravascular pressure is elevated above 140 mmHg, myogenic tone is decreased in cerebral arteries from SAH animals (i.e., vasodilation occurs). This reversal of pressure-induced constriction at supraphysiological intravascular pressures may represent an important mechanism in Triple H therapy currently used to improve clinical outcome in SAH patients.

METHODS

New Zealand White rabbits (males, 3.0–3.5 kg) were used in this study. All experiments were conducted in accordance with the Guidelines for the Care and Use of Laboratory Animals (NIH Publication 85-23, 1985) and followed protocols approved by the Institutional Animal Use and Care Committee of the University of Vermont.

Rabbit SAH model. Animals were initially anesthetized by isoflurane (5%) by using an induction chamber and then intubated and maintained on isoflurane (2–2.5%) anesthesia during the surgical procedure. A small (1.5–2.5 cm), longitudinal, midline suboccipital incision was centered over the foramen magnum, and the neck muscles were dissected until dural, midline suboccipital incision was centered over the

Angiography. Angiography was performed on animals before euthanasia on days 3, 5, or 7 post surgery (SAH day 3, 5, and 7). Angiography was also performed on control animals (no surgery, day 0). The animal (intubated and anesthetized by isoflurane) was positioned supine, and a 4-Fr angiographic catheter was inserted through the femoral artery. Under fluoroscopic guidance, the catheter was positioned into the aortic arch and then steered into the proximal subclavian artery and ultimately the vertebral artery. A static angiogram was then obtained by using a dental X-ray device (GE 100 model 11AA5A1, General Electric) during a 1.0- to 3.0 ml hand injection of contrast dye (Hydrape meglumine 60%, Winthrop Pharmaceuticals). Basilar artery diameter and an object of known dimension (included in each angiograph) were measured with imaging software (Image Pro, Media Cybernetics).

In vitro studies. Animals were euthanized (pentobarbital 130 mg/kg iv), and cerebral arteries were dissected in cold (4°C), oxygenated (95% O2-5% CO2) physiological saline solution (PSS) of the following composition (in mM): 118.5 NaCl, 4.7 KCl, 24 NaHCO3, 1.18 KH2PO4, 2.5 CaCl2, 1.2 MgCl2, 0.023 EDTA, and 11 glucose.

Morphological measurements. Basilar arteries were obtained from control and SAH day 3, 5, and 7 rabbits and immediately fixed in 3% paraformaldehyde, flash frozen, and stored at −80°C until sectioning (36). Ten-micron slices were treated with primary antibody (mouse anti-smooth muscle α-actin, 1:500 dilution) in PBS for 1 h at room temperature or overnight at 4°C. Sections were next treated with the secondary antibody, Cy3 goat anti-mouse IgG (1:500 dilution in 2% BSA/PBS) for 1 h at room temperature in darkness. Final washing of all slides was with the nuclear dye YOYO-1/ RNeasy (1:10,000/1:40 in PBS) for 10 min at room temperature.

Diameter measurements in isolated arteries. Cerebral artery segments obtained from branches of cerebellar or posterior cerebral arteries were cannulated on glass pipettes mounted in a 5-ml myograph chamber (Living Systems Instruments, Burlington, VT) and superfused with PSS aerated (20% O2-5% CO2-75% of N2) at 37°C and pH 7.4. Arteries were discarded if an initial constriction representing less than a 40% decrease in diameter was observed when arteries were exposed to 60 mM K+ PSS (isomotic replacement of NaCl with KCl). Diameter measurements were then recorded to step-wise increases in intravascular pressure. At the end of each experiment, passive (fully diluted) diameter measurements were obtained at each pressure in 0 Ca²⁺ PSS containing 50 μM diltiazem, a blocker of L-type voltage-dependent calcium channels. Initial experiments demonstrated that papavirine (200 μM), a potent smooth muscle relaxant, did not cause an additional dilation of arteries in the presence of 0 Ca²⁺ PSS containing diltiazem (n = 5, data not shown).

Organ culture of cerebral arteries. Cerebral artery segments 3–5 mm in length (100–200 μm in diameter) were isolated from control rabbits. Once blood was flushed from the lumen, arteries were transferred into Dulbecco’s modified Eagle’s medium-Ham’s F-12 medium amino acid solution supplemented with penicillin-streptomycin (1% vol/vol) and placed in an incubator at 37°C with 5.2% CO2 and 97% humidity. Arteries were organ cultured in the presence or absence of purified hemoglobin A₅ (oxygen form; 100 μM, Hemosol; Toronto, Canada). Spectrophotometric analysis determined that the oxyhemoglobin concentration was reduced by ~25% after 12 h of organ culture conditions (data not shown). Organ culture medium was changed at 12-h intervals. After 24 or 72 h, arteries were removed from the incubator and diameter measurements were determined (see above) in PSS containing 50 μM diltiazem with no oxyhemoglobin present. In some arteries the endothelium was removed by passing 1 ml of air and 2 ml of distilled water through the lumen before organ culture.

Statistical analysis. Data are presented as means ± SE. Pressure-induced constriction (myogenic tone) is expressed...
as a percent decrease of the fully dilated (passive) diameter of individual arteries at the same intravascular pressure (38). Distension ratios were obtained from passive diameter measurements and were calculated using the following equation (4): distension ratio = \( D_t / D_0 \), where \( D_t \) is the diameter of the artery in Ca\(^{2+}\)-free PSS containing 50 \( \mu \)M diltiazem, and \( D_0 \) is the diameter at zero pressure predicted by fitting passive diameter versus pressure for each artery to a third-order polynomial equation.

Statistical significance was considered at the level of \( P < 0.05 \) or \( P < 0.01 \) using Student’s t-test, Mann-Whitney’s rank sum test, or one-way analysis of variance followed by Student-Newman-Keuls multiple comparison test.

RESULTS

Angiographic and morphological examination of basilar arteries. Angiography was performed on control (day 0) and SAH animals (days 3, 5, or 7) to assess the degree of basilar artery narrowing that developed in our subarachnoid hemorrhage model (Fig. 1A). Basilar artery diameter was decreased by \( \sim 15\% \) in SAH day 3 animals (\( P < 0.05 \) vs. control) and \( \sim 25\% \) in day 5 and day 7 SAH animals (\( P < 0.01 \) vs. control) (Fig. 1B).

Immunohistofluorescence using the combination of a smooth muscle-specific \( \alpha \)-actin antibody and the nuclear stain YOYO-1 identified smooth muscle cells of these basilar arteries. The number of smooth muscle cell layers in basilar arteries from control (3.7 \( \pm \) 0.2 cells, \( n = 6 \)) and SAH day 7 (3.4 \( \pm \) 0.1 cells, \( n = 4 \)) animals was not significantly different (Fig. 1C). These data demonstrate a decrease in basilar artery diameter in our SAH model in the absence of smooth muscle hyperplasia.

Enhanced myogenic tone during SAH. To explore whether the function of small diameter (100–200 \( \mu \)m) cerebral arteries is altered during SAH, in vitro studies were designed to examine constriction to step-wise increases in intravascular pressure. As expected (10, 16, 35), an active constriction occurred in arteries isolated from control animals at intravascular pressures >40 mmHg (Fig. 2A). In similar arteries isolated from SAH animals, constriction was markedly enhanced at intravascular pressures between 40 and 100 mmHg (Fig. 2B). For example, pressure-induced constrictions at 80 mmHg were approximately twofold higher in SAH animals (e.g., 40.6 \( \pm \) 2.1\%, \( n = 5 \), day 5) compared with controls (19.7 \( \pm \) 2.2\%, \( n = 8 \)) (Fig. 3A). No significant difference in the level of constriction was observed among SAH groups day 3, day 5, or day 7. In a separate experimental series, cerebral arteries isolated from SAH day 5 animals were significantly more constricted than day 5 sham-operated or control animals at intravascular pressures of 80 and 100 mmHg (Fig. 3B).

In contrast to the marked differences in pressure-induced constrictions, passive physical properties of arteries obtained in the presence of 0 Ca\(^{2+}\) PSS and 50 \( \mu \)M diltiazem were similar among control and SAH groups (Fig. 4A). For example, the passive diameter at 10 mmHg (control: 121.8 \( \pm \) 7.5 \( \mu \)m, \( n = 8 \); SAH day 3: 114.5 \( \pm \) 14.7 \( \mu \)m, \( n = 5 \); SAH day 5: 126.9 \( \pm \) 9.6 \( \mu \)m, \( n = 4 \); SAH day 7: 112.4 \( \pm \) 8.8 \( \mu \)m, \( n = 4 \)) was not significantly different between groups. Cerebral artery distensibility, as indexed by distension ratios (4), was also similar between groups (Fig. 4B), suggesting a similar collagen and elastin content in these arteries. These data demonstrate that pressure-induced constrictions (myogenic tone) are significantly elevated in small diameter cerebral arteries from SAH animals in the absence of gross physical changes in the vascular wall.

Pressure-induced constrictions are enhanced in cerebral arteries organ cultured with oxyhemoglobin. Oxyhemoglobin released during the lysis of red blood cells has been implicated in the development of SAH-induced cerebral vasospasm (18, 25). To explore the ability of oxyhemoglobin to enhance pressure-induced constrictions in the cerebral vasculature, small diameter cerebral arteries obtained from control animals were organ cultured in serum-free media in the presence and absence of oxyhemoglobin (100 \( \mu \)M). Constrictions to 60 mM K\(^{+}\) were similar between arteries organ cultured in the presence and absence of oxyhemoglobin (Fig. 5A). However, pressure-induced constrictions were approximately twofold higher in arteries organ cultured with oxyhemoglobin (Fig. 5B). In some arteries following the organ culture period, \( \text{N}^\text{G} \)-nitro-L-arginine (L-NNA, 100 \( \mu \)M), a nitric oxide synthase inhibitor, was included in the PSS for 1 h before in vitro diameter measurements were obtained. When L-NNA was included in the PSS, arteries that were organ cultured for 24 h in the presence of oxyhemoglobin also exhibited significantly greater pressure-induced constrictions compared with arteries organ cultured for a similar period in the absence of oxyhemoglobin (Fig. 5C). In other arteries, the vascular endothelium was removed before organ culture. Endothelial-denuded arteries organ cultured with oxyhemoglobin also had enhanced pressure-induced constrictions (Fig. 5C). These data demonstrate that exposure of oxyhemoglobin to arteries during organ culture mimics the enhanced pressure-induced constrictions observed in our SAH model in a manner independent of nitric oxide generation or the vascular endothelium.

Reversal of myogenic tone in SAH animals by supra-physiological intravascular pressure. Elevation of systemic blood pressure plays an integral part in current therapy to improve cerebral blood flow in patients with SAH-induced cerebral artery vasospasm (2, 33). It has been hypothesized that high levels of intravascular pressure may override cerebral autoregulation. Given that constrictions are enhanced twofold in cerebral arteries isolated from SAH animals subjected to a physiological range of intravascular pressure (60–100 mmHg), we next examined the effects of step-wise increases in intravascular pressure up to 200 mmHg (Fig. 6). In arteries isolated from SAH (day 5) animals, increasing intravascular pressure from 100 to 120 mmHg did not result in a significant change in the diameter of these blood vessels. However, an increase in diameter was observed in cerebral arteries from SAH animals at intravascular pressures of 140 mmHg and above. At 200 mmHg, arteries from SAH animals
Fig. 1. Basilar artery diameter is decreased in a rabbit model of subarachnoid hemorrhage (SAH). A: representative angiographs from control (left) and day 5 SAH (right) rabbits. B: summary of basilar artery diameters measured from angiographs obtained from control (n = 8), SAH day 3 (n = 10), day 5 (n = 9), and day 7 (n = 5) animals. *P < 0.05, **P < 0.01. C: immunofluorescent images of basilar artery cross sections from control and SAH day 7 animals stained with anti-smooth muscle α-actin antibody and the nuclear dye YOYO-1. No significant difference (P > 0.05) was observed in the number of smooth muscle cell layers between control (n = 6) and SAH day 7 animals (n = 4).
were dilated to 91.6 ± 2.5% (n = 5) of their maximum diameter. Similar pressure-induced dilations were observed in control animals. For example, at 200 mmHg, cerebral arteries from control animals were dilated to 92.4 ± 2.0% (n = 5) of their maximum diameter. These data demonstrate that elevating intravascular pressure to 140 mmHg and above results in vasodilation of cerebral arteries from SAH animals.

**DISCUSSION**

In this study, we report the characteristics of small diameter cerebral arteries obtained from an animal model of SAH. Within a physiological range of intravascular pressures (i.e., 60–100 mmHg), pressure-induced constrictions were increased in arteries isolated from SAH animals compared with either control or sham-operated animals. These enhanced constrictions were reversed by increasing intravascular pressure above 140 mmHg. Arteries that were organ cultured in the presence of oxyhemoglobin also exhibited enhanced pressure-induced constrictions, independent of the vascular endothelium or nitric oxide synthesis. These results suggest that increased reactivity in small diameter cerebral arteries may play a role in the pathogenesis of decreased cerebral blood flow associated with SAH (Fig. 7). It is also possible that these small diameter arteries may be an important target of treatments such as Triple H therapy (33) currently used to improve clinical outcome in SAH patients.

Alterations in cerebral autoregulation after SAH: role of small diameter arteries. One remarkable feature of the cerebral circulation is the ability to maintain constant blood flow despite fluctuations in cerebral perfusion pressure, a phenomenon often referred to as cerebral autoregulation [(20), Fig. 7]. To achieve stable cerebral blood flow during changes in blood pressure,
cerebral arteries must constrict in response to intravascular pressure elevations and dilate when intravascular pressure is reduced. As evidenced in Fig. 2, elevations of intravascular pressure within a physiological range (60–100 mmHg) will constrict isolated cerebral artery segments in the absence of other vasoactive stimuli. Pressure-induced constrictions, first described by Bayliss (3), have also been termed myogenic tone (14). Poiseuille’s law states that the flow through a cylinder is a fourth-order function of radius, suggesting small changes in arterial diameter can have a great impact on blood flow. Thus the enhanced pressure-induced constrictions observed in our SAH model could potentially result in a substantial decrease in blood flow through affected regions of the cerebral vasculature.

SAH-induced vasospasm is generally identified by large diameter (>1 mm) arterial narrowing observed with angiography. The severity of angiographically defined vasospasm typically corresponds to the amount of blood released into the subarachnoid space during

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Fig. 4. Passive physical properties are similar between isolated cerebral arteries from control and SAH animals. A: passive diameter measurements of isolated cerebral artery segments at intravascular pressures from 10 to 100 mmHg. Measurements were made in maximally dilated arteries (0 Ca²⁺ PSS + 50 μM diltiazem). B: summary of distension ratios calculated for each group.

Fig. 5. Pressure-induced constrictions are enhanced in cerebral arteries organ cultured in the presence of oxyhemoglobin. A: summary of K⁺-induced constrictions in cerebral arteries organ cultured for 24 h or 72 h in the presence and absence of oxyhemoglobin (OxyHb, 100 μM). Measurements were obtained at 10 mmHg, and constrictions are expressed as a percent decrease in diameter. B: summary of pressure-induced constrictions in cerebral arteries organ cultured in the presence and absence of OxyHb for a period of either 24 or 72 h. Measurements were obtained at 100 mmHg, *P < 0.05, unpaired Student’s t-test. C: summary of pressure-induced constrictions in cerebral arteries organ cultured for 24 h in the presence and absence of OxyHb. Nω-nitro-L-arginine (L-NNA, 100 μM), an inhibitor of nitric oxide synthesis, was not included in organ culture media but rather added to the PSS for 1 h before in vitro diameter measurements were obtained. Endothelium was removed by passing 1 ml of air and 2 ml of distilled water through the lumen before organ culture. **P < 0.01, *P < 0.05, unpaired Student’s t-test.
aneurysm rupture (8). However, the degree of angiographically defined vasospasm does not always correlate with the degree of neurological deficits (symptomatic vasospasm) observed in SAH patients (13, 24, 33). A number of recent studies have suggested that vasoconstriction of small diameter arteries may also contribute to the manifestation of neurological deficits resulting from subarachnoid hemorrhage. For example, magnetic resonance imaging (MRI) has recently been used to describe ischemic cerebral lesions in SAH patients that were likely the result of small diameter vasospasm (27). Measurements of cerebral circulation time and regional cerebral blood flow also suggest increased resistance (constriction) of small diameter cerebral arteries of SAH patients (24). Cerebral blood flow was found to be decreased in SAH patients independent of changes in intracranial pressure or large artery (angiographic) vasospasm (17). Using a primate SAH model, Takeuchi and colleagues (30) examined the relationship between cerebral blood flow and graded changes in blood pressure. Their finding of altered cerebral blood flow autoregulation is in close agreement with our observed enhancement of pressure-induced constrictions in small diameter cerebral arteries from our rabbit SAH model.

Potential mechanism of enhanced pressure-induced constrictions after SAH: role of oxyhemoglobin. Our data demonstrate enhanced pressure-induced constrictions when cerebral artery segments were organ cultured in the presence of oxyhemoglobin (Fig. 5). These results suggest oxyhemoglobin may also play a role in the enhanced pressure-induced constrictions observed in cerebral artery segments isolated from our SAH model. Oxyhemoglobin can inhibit endothelium-dependent vasodilation by acting as a scavenger of nitric oxide (22). However, we have found that organ culture of cerebral arteries with oxyhemoglobin results in enhanced pressure-induced constrictions independent of the vascular endothelium or nitric oxide synthesis. In vitro cerebral artery contraction to the direct application of oxyhemoglobin has also been shown to occur in the absence of the vascular endothelium (32). These results suggest that although SAH-induced cerebral vasospasm may occur in part through inhibition of endothelial function, oxyhemoglobin can have direct effects on the vascular smooth muscle of small diameter cerebral arteries.

We have found that the enhanced pressure-induced constrictions observed in this study were abolished by a combination of diltiazem and Ca²⁺-free PSS; however, the exact cellular mechanism(s) involved in this phenomenon remains to be elucidated. Graded increases in intravascular pressure have been shown to cause membrane potential depolarization and enhanced Ca²⁺ entry through L-type voltage-dependent Ca²⁺ channels in isolated cerebral arteries (5, 10, 16). It has recently been proposed that activation of transient receptor potential nonselective cation channels may underlie pressure-induced membrane depolarization.

Fig. 6. Supraphysiological intravascular pressure dilates cerebral arteries from control and SAH animals. A: in vitro diameter measurements of an isolated cerebral artery obtained from a SAH day 5 animal subjected to step-wise increases in intravascular pressure from 100 to 200 mmHg, as indicated by horizontal black bars. Vasodilation was observed when intravascular pressure was elevated above 120 mmHg. B: summary of data illustrating the degree of cerebral artery constriction as intravascular pressure was elevated from 100 to 200 mmHg.

Fig. 7. Schematic illustration of hypothetical alterations in the regulation of cerebral blood flow following SAH. Within a physiological range of intravascular pressures, pressure-induced constrictions are enhanced following SAH leading to a decrease in cerebral blood flow. However, when intravascular pressure is elevated above the autoregulatory range (i.e., >140 mmHg), pressure-induced constrictions are reversed and cerebral blood flow increases.
tions in the cerebral vasculature (37). Membrane depolarization following SAH could also occur due to decreased K⁺ channel conductance resulting from enhanced production of 20-HETE (12, 15). Thus membrane depolarization through a number of mechanisms may be involved in the potentiation of pressure-induced constrictions observed in the present study. However, enhanced Ca²⁺ entry through a pathway distinct from L-type voltage-dependent Ca²⁺ channels cannot be excluded by our present data. In addition, increased activity of protein kinase C and Rho kinase has been reported in other SAH models (19, 26), which could lead to increased myosin light chain phosphorylation and increased Ca²⁺ sensitivity of the contractile apparatus in cerebral vascular smooth muscle.

Reversal of pressure-induced constriction by supraphysiological intravascular pressure: implications for Triple H therapy. We observed that arteries from control and SAH arteries dilated when intravascular pressure was elevated above 140 mmHg (Fig. 6). Cerebral artery dilation in response to supraphysiological levels of intravascular pressure has been referred to as “forced dilatation” or “autoregulatory breakthrough” (6). During Triple H therapy, systolic blood pressure is often elevated in the range of 180–220 mmHg; thus intravascular pressures within cerebral arteries are likely to exceed 140 mmHg. Our data are consistent with the hypothesis that the effectiveness of hypervolemia, hemodilution, and hypertension (Triple H) therapy currently used in the treatment of the symptoms associated with cerebral vasospasm may result from increased cerebral blood flow associated with dilation of small diameter arteries in response to supraphysiological intravascular pressure.

In conclusion, these data suggest that in the days following SAH, pressure-induced constriction (myogenic tone) is enhanced in small diameter cerebral arteries subjected to physiological levels of intravascular pressure. However, supraphysiological intravascular pressures cause vasodilation, suggesting small diameter cerebral arteries may act as therapeutic targets of Triple H therapy used in the treatment of cerebral artery vasospasm.

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